Briefing on Antibiotics for OCSPP Deputy Assistant Administrators

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Antibiotics as Agricultural Use Bactericides

- There are 3 antibiotic active ingredients currently registered for agricultural use in the United States:

Active Ingredient	Class of Compound	Year Registered	Registered Uses
Streptomycin	aminoglycoside	1955	• Pome fruit, beans, greenhouse seedlings (celery, pepper, tomato), potato seed piece, tobacco, ornamental, homeowner garden • Current citrus Section 18 use approved in Florida through 12/31/2017
Oxytetracycline	tetracycline	1974	• Apple, pear, peach, nectarine, nonagricultural uses (forest tree injection, ornamentals, non crop bearing trees, shrubs, palms • Current citrus Section 18 use approved in Florida through 12/31/2017
Kasugamycin	aminoglycoside	2014	• Pome fruit group (time-limited registration expiring 12/31/2018)

- Both Streptomycin and Kasugamycin are also approved for use by PMRA (Canada) for certain uses.
- Of these active ingredients, both streptomycin and oxytetracycline also have human and animal drug uses approved with the Federal Drug Administration (FDA). Kasugamycin is not used for human or veterinary medical purposes.

Currently Pending New Uses with the Office of Pesticide Programs (OPP)

- Streptomycin
  - 1 action submitted by The Interregional Research Project No. 4 (IR-4)/Geologic Corporation/Agrosource Inc on grapefruit, tomato (field plus expanded greenhouse use), and conversion of pome fruit crop group 11 to 11-10.
  - 1 petition submitted by Geologic Corporation/Agrosource Inc. on citrus crop group 10-10
- Oxytetracycline
  - 1 petition submitted by Geologic Corporation, Agrosource Inc. for uses on citrus crop group 10-10
  - 1 petition submitted by Nufarm Americas, Inc. on citrus crop group 10-10*
  - 1 petition submitted by Nufarm Americas, Inc. on cherry*

    *these petitions are on a later review schedule
- Kasugamycin
  - 1 petition submitted by IR-4, Arysta LifeScience North America LLC for uses on walnut and cherry subgroup 12-12a

Registration Review

- Only streptomycin and oxytetracycline are in this round of registration review; kasugamycin was registered in 2014
- Assessments from HED and EFED are complete, ARRT assessment pending
- All assessments are scheduled to be published in June 2018
- Proposed Interim Decisions scheduled to be completed in March 2019, with Interim Decisions scheduled to be completed in September 2019

The Rationale for Antibiotic Use in Agriculture

- There are few registered alternatives for most bacterial infections in crops. Different modes of action (MOAs) would help reduce the potential for resistance to develop in any current conventional/biopesticide tools approved.
- Huanglongbing (HLB), also known as citrus greening disease, is one of the world's most serious citrus diseases, with no known cure.
- Walnut growers/groups have reached out to the Agency over the past year greatly supporting the proposed use for kasugamycin on walnut to control walnut blight and have requested an expedited review.
- Over the past 10 years, numerous sections 18 emergency exemptions have been issued to various States for the use of antibiotics (kasugamycin, gentamycin, oxytetracycline, and streptomycin) on pome fruit and citrus to address different diseases such as fire blight, citrus canker and HLB.

How Antibiotic Assessments Differ from Conventional Pesticide Assessments

- Conventional pesticide assessments comprise of:
  - Human health risk assessment
    - Toxicology, Occupational Exposure, Residue Chemistry
  - Ecological risk assessment
    - Environmental fate and effects
  - Benefits review
    - Efficacy, alternatives comparison
- In addition to these, antibiotic assessments also include:
  - Antibiotic resistance review based on FDA's Guidance to Industry #152 assessment with the addition of active ingredient specific isolate study review
  - Federal Partner consultation with the FDA/CDC/USDA on our antibiotic resistance reviews
  - Review of Resistance Management proposal from the Registrant including label language review, efficacy, and review of proposals for educational materials/stewardship plan

How Antibiotic Assessments Differ from Conventional Pesticide Assessments (Cont'd)

- Generally speaking, the antibiotics registered for agricultural use have no traditional human health risk assessment concerns and few ecological risk concerns. Instead, our concerns come from the possibility of agriculture bactericide use contributing to antibiotic resistance developing in humans and plants

Antibiotic Resistance Effects

- At least 2 million people acquire serious antibiotic-resistant infections each year
  - At least 23,000 people die each year as a direct result of these antibiotic-resistant infections
- Almost 250,000 people each year require hospital care for *C. difficile* infections
  - At least 14,000 people die each year in the United States from *C. difficile* infections
- Antibiotic-resistant infections add costs to the already overburdened U.S. healthcare system
  - Antibiotic-resistant infections usually require long, costly treatments, extended hospital stays
- Total economic cost of antibiotic resistance to the U.S. economy estimates vary but have ranged as high as $20 billion in excess direct healthcare costs

How Resistance Develops

- Bacteria will inevitably find ways of resisting antibiotics
- Bacteria may adapt to become resistant to an antibiotic by
  - Restricting access of the antibiotic to the cell or using pumps to keep antibiotic drugs from entering
  - Destroying the antibiotic by using enzymes to break down the antibiotic drug and make it ineffective
  - Changing the antibiotic by using enzymes to alter the antibiotic drug so that it loses its effectiveness
  - Developing different and new processes to get around those disrupted by the antibiotics
- Often, resistance genes are within plasmids, pieces of DNA that can move between bacterial species
  - Enables the spreading of resistance from one bacteria to another
- CDC believes aggressive action is needed now to keep new resistance from developing and to prevent the resistance that already exists from spreading

Antibiotic Resistance Review Team (ARRT) Assessment

- Qualitative risk assessment evaluating the probability of antibiotic resistance in microbes of human health concern based on FDA's 152 guidance to industry for antibiotic use in food animals, with modifications appropriate to agricultural chemicals.
- Assessment categories: release, exposure, consequence.
- These three elements provide an overall qualitative risk estimate

ARRT Assessment Criteria

- RELEASE ASSESSMENT

(rating scale: low, medium, or high)

Product chemistry, Resistance mechanisms in microbes, Transfer of resistance, Selection Pressure

- EXPOSURE ASSESSMENT

(rating scale: low, medium, or high)

Food contamination of crop, Food Commodity Consumption, Acreage treated

- CONSEQUENCE ASSESSMENT

(rating scale: important, highly important, critical)

Rating of Clinical Importance of Antibiotic

- RISK ESTIMATION

(rating scale: low, medium, high)

Integrates the components of the 3 assessments into an overall qualitative conclusion

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ARRT Assessment Outcomes
Streptomycin- Citrus Crop Group 10-10

Release rating: **high**

- Clinical microbe resistance common & mobile; interaction with environmental isolates; expanded acreage

Exposure rating: medium

- Increased acreage, citrus food commodity being consumed is high; contamination and food poisoning incidents are low

Consequence rating: highly important

- Member of aminoglycoside group, currently used in treatment of bacterial diseases and infections

"Medium" qualitative risk estimation rating

Uncertainties: information is lacking on presence of bacteria associated with food borne disease in citrus orchards and the movement of traits from the target and epiphytic bacteria to bacteria of concern for human health. For the exposure assessment, data on the actual level of contamination with bacteria of human concern on citrus and citrus commodities are not available.

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ARRT Assessment Outcomes- Streptomycin- Tomato (field, expanded greenhouse)

Release rating: **high**

- Presence of resistance in targeted species and microbes of human health concern; mobile

Exposure rating: medium

- 1-day PHI, MRL increase; high amounts of tomato consumption, low contamination serious consequences

Consequence rating: highly important

- Member of aminoglycoside group, currently used in treatment of bacterial diseases and infections

"Medium" qualitative risk estimation rating

Uncertainties: presence of bacteria causing foodborne illness in field tomato (e.g., *E.coli* and *Salmonella* species); probability streptomycin residues select for multidrug resistant forms of these bacteria; the movement of resistance traits from the target and epiphytic bacteria to bacteria of concern for human health. Although fresh tomato has been associated with foodborne illness, the actual level or source of contamination is often an uncertainty.

ARRT Assessment Outcomes- Oxytetracycline- Citrus Crop Group 10-10

Release rating: **high**

- Resistance in clinical microbes common & mobile; interactions with environmental isolates; expanded acreage

Exposure rating: medium

- Increased acreage, citrus food commodity consumption high; contamination of citrus and food poisoning incidents are low

Consequence rating: highly important

- Member of tetracycline group, currently used in treatment of bacterial diseases and infections

"Medium" qualitative risk estimation rating due to greatly expanded acreage for Citrus canker and Citrus Greening

Uncertainties: limited information for resistance selection & mobility associated with environmental isolates. No robust information in public literature on rate of transfer for tetracycline resistance.

ARRT Assessment Outcomes- Kasugamycin- Walnut, Cherry Subgroup 12-12a

Release rating: low

- Low selection for cross resistance to other antibiotics; not effective against human pathogenic species

Exposure rating: low

- Level of food commodity contamination low but variable; food poisoning incidents low

Consequence rating: important

- Lowest risk rating, field data shows no change in resistance frequency to other aminoglycosides in presence of kasugamycin resistance in bacteria; no clinical uses, different binding site in bacterial protein translation

Overall risk estimation: "Low"

- Lab data on lack of cross-resistance is confirmed by field monitoring data to date.
- Uncertainties: No definitive data to cite for the resistance transfer endpoint. Information lacking on kasugamycin susceptibility for the range of bacteria associated with food borne incidents in crops proposed. Rating could change if agricultural use does co-select for resistance to other clinically important antibiotics in the future.

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Stewardship of Antibiotics

- Managing antibiotic resistance is critical to keeping antibiotics working
- OPP assessments consider resistance in the bacteria causing the plant disease and the potential contribution to antibiotic-resistant diseases in humans
- Human pathogens and plant pathogens may exist together, so that resistance may develop in human pathogens as a result of antibiotic use on crops
  - Pathogens rarely share the same hosts
- For pesticides, resistant species in or on food, the skin of workers, or indirectly through the environment or clothing can spread resistance.
- By minimizing these three routes of exposure, EPA hopes to minimize the growth or spread of resistant microbes on humans or on the crop.

Federal Response To Antibiotic Resistance

- Other agencies (CDC, FDA, USDA) work in their areas of expertise
- CDC cites "Improving Antibiotic Prescribing/Stewardship" as one of its Four Core Actions to Fight Resistance
- FDA is committed to antimicrobial stewardship, fostering stewardship and assessing impact of intervention strategies in veterinary settings
- USDA funds research to study the role of agriculture in antimicrobial resistance and identifying alternative strategies to mitigate antimicrobial resistance in the food chain

EPA's Response to Antibiotic Resistance

- EPA shares USDA's goal of "reducing potential negative impacts from the use of antibiotics, and identifying alternative strategies for mitigating [antibiotic resistance] in the food chain."
- EPA believes that the management of pesticide resistance development is an important part of sustainable pest management
- In support of these goals, EPA is assessing the potential development of antibiotic resistance as an adverse effect under FIFRA.

Federal Partner Consultation

- Key comments from the cross-agency interactions were:
  - Kasugamycin use preferred over streptomycin and oxytetracycline as it does not currently select for cross-resistance to antibiotics important for human health
  - Align with
    - FDA – Judicious use of antimicrobial drugs
    - WHO Global Action Plan on Antimicrobial Resistance
  - Precaution necessary to limit cross-resistance/selection pressure.
  - Despite history of streptomycin use in agriculture, CDC and FDA would prefer to restrict additional usage
  - Concern for occupational exposure for all antibiotics used in agriculture
  - Drift to neighboring fields/bodies of waters should be prevented
  - Prescribed, limited usage based on need

Ongoing International Work

- **Codex Alimentarius Commission (Codex)** is a Joint FAO/WHO Food Standards Program that harmonizes international food safety standards and helps facilitates trade.
- In December 2016, Codex established the **Task Force on Antimicrobial Resistance (TFAMR)**. The objective of TFAMR is to establish science-based guidance on the human health risk associated with antimicrobial resistance in different areas of use of antimicrobials, including veterinary applications, plant protection and food processing.
- TFAMR recently issued a **data call on antimicrobials used in plant protection** and has requested -- through the Codex Committee on Pesticide Residues -- **guidance on data sources that characterize use practices of pesticides that may contribute to antimicrobial resistance**.

Benefits of Antibiotics for Plant Uses

- OPP assesses the benefits of pesticides to the user and considers target pests and alternative control methods
- The benefits of new uses of antibiotics can vary depending on several factors
  - Especially, the ability of the grower to acceptably manage a disease by other methods (including registered pesticides)
  - Severity and incidence of the disease
- Bacterial diseases of crops can be difficult to manage
  - Occur sporadically and depend on weather conditions, especially humidity, temperature, and wetness
- Generally, antibiotics can reduce effects of, but do not cure, plant disease
  - For citrus, antibiotics would be most effective when applied to replacement trees prior to development of severe disease symptoms

Benefits of Antibiotics for Plant Uses (cont.)

- No pesticides are registered to manage HLB in citrus
  - Symptoms include leaf and fruit drop, off-tasting fruit, and lower yields
  - Pesticide use has focused on controlling the Asian citrus psyllid which vectors the disease
- There would likely be a benefit to citrus growers as data indicate that adverse symptoms can be reduced
- Conversely, for tomato or walnut there may be low benefits since current management strategies appear to be equally effective to antibiotics
- In general, the new uses proposed for antibiotics provide additional modes of action to help manage plant resistance development to registered pesticides
  - Rotating different chemistries can delay development of resistance to any individual chemistry
  - Copper products are standard treatments for bacterial diseases, but phytotoxicity and resistance can be problematic

Kasugamycin, Oxytetracycline and Streptomycin: A Comparison

- In general, CDC/FDA and USDA have concerns for the expansion of antibiotic agricultural bactericide use due to resistance concerns. However, the preference is for kasugamycin use over streptomycin or oxytetracycline as kasugamycin is not approved for human or veterinary medical uses and does not co-select for resistance to other clinical antibiotics.
- Oxytetracycline and streptomycin have confirmed resistance in human isolates tested by CDC.
- Oxytetracycline and streptomycin have similar heightened resistance concerns as compared to kasugamycin. However, both oxytetracycline and streptomycin would have a high benefit for use in citrus due to the HLB crisis. Kasugamycin has not been demonstrated as an efficacious tool to use for treatment of HLB in citrus.
- Additional streptomycin tomato use concerns:
  - Incidental soil exposure has possibility to increase selection pressure due to low to ground application
  - Short PHI (1 day) coupled with first order half-lives between 13-49 days increases occupational exposure concern in regards to resistance
  - Highly consumed crop with incidents of food borne illness associated with the crop- soil residues anticipated to be relatively high on harvested crops
  - Low benefit due to multiple effective registered alternatives

Overall Resistance Concerns Identified For All Three Antibiotics

- EPA and our Federal Partners have concerns for:
  - Impact of agricultural use on increasing selection pressure resulting in increased resistance (both in humans and plants)
  - sub-therapeutic antibiotic exposure to occupational workers through agricultural use
  - drift/exposure away from target application site

Mitigating Resistance Concerns: Proposal

- Label statements
  - Additional personal protective equipment
  - Grazing restrictions
  - Restriction against use of animal manure or human biosolids for fertilizer
  - Statements to limit off-target exposure (aerial restrictions, chemigation/irrigation)
  - Prescribed use
- Time limited (7 year) new use registrations
  - Monitoring (oxytetracycline and streptomycin only at this time)
  - Implementation of stewardship plans including education/training and scouting for incidences of resistance
  - Evaluation of how use is expanding by receipt of sales reports from Registrants
  - Re-evaluation with Federal Partners after 6 years to update current risk picture in regards to resistance

Regulatory Rationale

- Risk-benefit decision including review of benefits/alternatives
- Lack of performance and new cases of suspected/confirmed plant resistance may not be immediately identifiable after application, but rather after multiple seasons of applications. Therefore, time-limited registrations on new uses will allow for a more complete picture of evolving resistance trends. Monitoring will also inform on this, as will additional consultation with our Federal Partners
- Growers/users will gain knowledge of useful strategies to slow the development of resistance to plant pathogens and prolong the useful life of antibiotic products on agricultural crops through education/training/stewardship
- Additional protection for workers, reduction of off-target exposure, and reduced potential for resistance through additional label restrictions

Remaining Steps

- Begin public process (30 day comment period) for:
  - Oxytetracycline citrus crop group 10-10 petition
  - Kasugamycin walnut and cherry subgroup 12-12a petition
  - Streptomycin citrus crop group 10-10 petition/Grapefruit and pome fruit crop group expansion
- Reach agreement with Registrants on Agency proposed decision implications including label mitigation and terms of registration
  - includes contacting the Registrant for streptomycin to request withdrawal of tomato use
- Continue to work with the California Department of Pesticide Regulation on an efficient tandem review to allow product to get into the hands of the walnut growers as soon as possible
- Incorporate comment responses into Final Decision document
- Publish tolerances in the Federal Register
- Approval of labels

Current PRIA due dates

Active Ingredient	Petitioner/Registrants	Proposed Uses	Current PRIA due date
Oxytetracycline	Agrosource Inc./Geologic Corp.	Citrus crop group 10-10	2/13/2018
	Nufarm Americas Inc.	Citrus crop group 10-10	1/18/2018*
	Nufarm Americas Inc.	cherry	5/9/2018*
Streptomycin	IR-4/Agrosource Inc./Geologic Corp.	Grapefruit/tomato/pome fruit crop group conversion	4/3/2018
	Agrosource Inc./Geologic Corp.	Citrus crop group 10-10	4/3/2018
Kasugamycin	IR-4/Arysta LifeScience North America Inc.	Walnut, cherry subgroup 12-12a	1/16/2018

*The Nufarm America's Inc. petitions will be renegotiated to later in 2018 (end of FY2018).